Avigen Recommendation

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Current Data and Assumptions

- Procedure is well-tolerated.
- Predictive value of animal models with respect to IGLT is unclear.
- Motile sperm fraction may be positive as the dose increases.
- At current rate and clinical hold triggers, the Phase I could take an additional 5 years to complete.
- Limiting enrollment to subjects that are unable to reproduce will further delay completion of trial and the usefulness of the clinical data.
- Higher doses may yield therapeutic levels of FIX based on preclinical data.

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Informed Consent is a Reasonable and Prudent Safeguard Against IGLT

- Subject is educated on the potential risk of germline transmission.
- Subject is advised to use barrier contraceptives.
- ~~Risk of germline transmission is low.~~
- Subject is regularly monitored for positive semen and positive motile sperm.
- Germline transmission can be avoided by sperm banking.

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Avigen's Recommendation to the BRMAC Committee

- Avigen should continue its assay development and preclinical studies in various animal models.
- Informed consent should be reviewed and updated as needed to reflect current data.
- Phase I trial should be allowed to continue regardless of whether motile sperm fraction is positive.
- Subject should be monitored until three consecutive semen samples, taken at least 1 month apart, are negative.
- Continue semen fractionation to determine whether vector sequences are in motile sperm.

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Avigen's Recommendation to the BRMAC Committee

- Determine whether vector sequences in the semen are biologically active.
- Use clinical data to identify predictive IGLT preclinical models.
- ~~Continue to encourage subjects to bank sperm prior to treatment.~~
- Subjects are informed of the semen results and counseled whether to continue contraception.
- Subject and partner encouraged to undergo counseling on a regular basis if vector sequences are persistent (greater than 1 year) in motile sperm or are persistently infectious.

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